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Effects of Acute Abstinence, Reinstatement, and Mecamylamine on Biochemical and Behavioral Measures of Cigarette Smoking in Schizophrenia

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Abstract

Background: Schizophrenics have higher rates of smoking than the general population, and more difficulty with smoking cessation. However, there has been little study of differences between schizophrenics and controls with respect to biochemical and behavioral indices of smoking. We compared smokers with schizophrenia (SS; n=27) and control smokers (CS; n=26) on smoking and psychiatric outcomes at baseline, during acute smoking abstinence and reinstatement, and with pre-treatment using the nicotinic acetylcholine receptor (nAChR) antagonist mecamylamine (MEC) in a human laboratory setting.

Methods: Biochemical (e.g., plasma nicotine) and behavioral (e.g., craving, withdrawal) outcomes were assessed at baseline, after overnight abstinence, and after smoking reinstatement during three consecutive test weeks. Each week, participants received one of three doses of MEC (0.0, 5.0, or 10.0 mg/day × 3 days) in a randomized, counterbalanced manner.

Results: Compared to CS, SS displayed similar levels of craving and withdrawal, but higher plasma nicotine and cotinine levels, and cotinine/CPD ratio. During reinstatement, SS consumed significantly more cigarettes than CS, but MEC did not significantly alter indices of smoking, psychiatric symptoms, or cigarette consumption during reinstatement.

Conclusions: 1) The reinforcing effects of smoking may be increased in SS versus CS after overnight abstinence; 2) the lack of effects of nAChR antagonism may suggest that non-nicotinic components of cigarettes may contribute to the behavioral effects of smoking in both SS and CS; and 3) consistent with previous studies, SS may exhibit higher baseline levels of nicotine and cotinine, and greater extraction of nicotine per cigarette than CS.

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Keywords

nicotinic acetylcholine receptor; mecamylamine; cigarette smoking; nicotine withdrawal; tobacco craving; schizophrenia

1. INTRODUCTION

Patients with schizophrenia have a higher prevalence of smoking (58-88%; Kalman et al., 2005; de Leon and Diaz, 2005) than the general population (25%; Vocci and DeWit, 1999), greater dependence on nicotine, and more difficulty with smoking cessation (Dalack et al., 1998; de Leon et al., 2002; Hughes et al., 1986; Ziedonis and George, 1997). Consequently, these patients experience earlier morbidity and mortality (Lichtermann et al., 2001), and reduced quality of life as a result of their recalcitrant smoking behavior (Dalack et al., 1998; Ziedonis et al., 2003).

A number of reasons have been proposed to explain why patients with schizophrenia may smoke at a higher rate and have more difficulty quitting. For example, Spring et al. (2003) found that smokers with schizophrenia attributed greater benefits to smoking and believed that they would need more incentives to quit than controls. In addition, schizophrenia is associated with neurocognitive deficits in attention, executive function, and spatial working memory (Keefe et al., 1995; Park and Holzman, 1992) and patients may smoke at higher rates to remediate these deficits (Adler et al. 1993; George et al., 2002a; Sacco et al., 2005; Smith et al., 2002). It has been shown that acute smoking reversed abstinence-induced impairment of visuospatial working memory and sustained attention selectively in patients with schizophrenia compared to controls, and that performance enhancement was dependent on nicotinic receptor stimulation (Sacco et al., 2005).

However, little is known about how smokers with and without schizophrenia differ on specific aspects of smoking behavior. Several studies have suggested that smokers with schizophrenia had higher levels of urinary (Olincy et al., 1997), saliva (Strand and Nybäck, 2005), and plasma cotinine (Sacco et al., 2005; Williams et al., 2005) than control smokers despite no significant difference in daily smoking or urinary cotinine clearance (Olincy et al., 1997), or in metabolism of cotinine (Williams et al., 2005). A recent study suggesting differences in smoking topography in smokers with schizophrenia versus controls provides physiological support for increased nicotine intake (Tidey et al., 2005). Information about the similarities and differences between smokers with and without schizophrenia can be used to improve smoking cessation interventions.

The current study was a secondary analysis derived from a parent investigation of smoking, nicotinic acetylcholine receptors (nAChRs) and cognitive function in smokers with and without schizophrenia (Sacco et al., 2005). The primary cognitive outcomes have been reported elsewhere (see Fonder et al., 2005; Sacco et al., 2005; Sacco et al., 2006; George et al., 2006). The aims of this study were to compare biochemical and behavioral indices of cigarette smoking in smokers with and without schizophrenia: 1) at smoking baseline, and; 2) while undergoing acute abstinence and reinstatement in a controlled human laboratory setting. Additional aims were; 3) to determine the effects of smoking abstinence and reinstatement on psychotic and depressive symptoms, and; 4) to examine the effects of nAChR blockade on these measures using pretreatment with mecamylamine (Inversine®), a non-selective centrally-acting nAChR antagonist. We predicted that: 1) there would be baseline differences on biochemical and behavioral indices of smoking between schizophrenic and control smokers; 2) that such differences would also be observed after overnight abstinence and reinstatement; 3) that psychotic and depressive symptoms would not be altered by overnight abstinence and

reinstatement; 4) that MEC would increase tobacco consumption, withdrawal and craving in both schizophrenic and control smokers, both at baseline and with overnight abstinence and smoking reinstatement.

2. METHODS

2.1 SUBJECTS

Seventy-eight smokers with schizophrenia (SS) and eighty-two control smokers (CS) were screened. Exclusions for SS (n=46) and CS (n=54) included: positive urine drug screens (SS, n=15; CS, n=23), an IQ score lower than the minimum (80) required (SS n=0; CS n=1), logistical problems (SS, n=3; CS, n=3), diagnostic ineligibility (SS, n=3; CS, n=2), medical exclusions (SS, n=6; CS, n=0), failure to meet nicotine dependence criteria (SS, n=8; CS, n=15), and unwillingness to participate in the study after eligibility determination (SS=11; CS=10). After baseline evaluations, n=32 SS and n=28 CS were enrolled and n=27 SS and n=26 CS completed the entire study without protocol violations. Written informed consent was obtained from all participants, and the protocol was approved by Yale Medical School's Human Investigation Committee.

Participants were evaluated using the Structured Clinical Interview for DSM-IV (SCID-IV) Axis I Disorders (First et al., 1996). SS were clinically stable outpatients prescribed a stable dose of antipsychotic medication (typical or atypical) for at least three months prior to study assessments. CS demonstrated no current Axis I disorders. Participants consumed ≥ 15 cigarettes per day with expired breath carbon monoxide (CO) levels ≥ 10 ppm and plasma cotinine levels ≥ 150 ng/ml. Subjects met DSM-IV criteria for nicotine dependence and had a score of ≥ 5 on the Fagerström Test of Nicotine Dependence (FTND; Heatherton et al., 1991).

2.2 PROCEDURES

Following baseline assessment, participants completed weekly test sessions spanning three consecutive days per week during three separate test weeks, and included four laboratory sessions (see Figure 1 and Sacco et al., 2005). Participants received each of three MEC doses (0.0, 5.0, 10.0 mg/day) in a randomized, counterbalanced manner. On the first testing day (Day 2AM), subjects completed study assessments prior to the neurocognitive testing session. Subjects remained abstinent after 8:00 pm on the evening of Day 2. The Day 3AM testing session began after verification of overnight abstinence by CO level <10 ppm. Following the testing session, subjects were instructed to "smoke until you are satisfied" during a 1-hour smoking reinstatement period (1200-1300h) after which the final testing session occurred (Day 3PM).

Contingency reinforcement was used to facilitate overnight smoking abstinence (Sacco et al., 2005). Subjects who failed to achieve abstinence after two attempts were excluded from further participation. Five subjects were required to repeat a test week because they failed to obtain overnight smoking abstinence (SS, n=3; CS, n=2). Psychotropic medications of SS were held during testing sessions to minimize medication effects on acute smoking behavior.

2.3 MEASURES

2.3.1 Cigarette Smoking Measures

2.3.1.1 Smoking Consumption To determine daily smoking, a timeline followback (TLFB; Sobell et al., 1988) for the previous 7 days was administered at baseline. Smoking during the *ad lib* 1-hour reinstatement period was verified through direct observation by research staff. Biochemical measures of smoking included expired breath carbon monoxide (CO) level

determination [Bedfont EC50 Microsmokerlyzer II, Kent, UK] and plasma cotinine and nicotine levels.

2.3.1.2 Craving and Withdrawal The Minnesota Nicotine Withdrawal Scale (M-NWS; Hughes and Hatsukami, 1986) was administered at the beginning of each testing session to assess DSM-IV symptoms of tobacco withdrawal including craving for nicotine, irritability, and anxiety. The Tiffany Questionnaire for Smoking Urges (T-QSU; Tiffany and Drobes, 1991) was administered at the beginning of each testing session to assess urges to smoke in response to two affective systems: 1) positive affect related to expectancy of reinforcement (Factor 1) and; 2) the expectancy of a reduction of withdrawal related negative affect (Factor 2). Recent work has suggested that these measures are reliable for use with smokers with schizophrenia (α 's=0.79-0.88; Weinberger et al., 2006).

2.3.1.3 Nicotine Dependence The Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) was administered once during the screening process. The reliability of the FTND has been found to be adequate for SS and comparable to CS (Weinberger et al., 2006).

2.3.2 Psychiatric Symptoms and Adverse Events

2.3.2.1 Depression The Beck Depression Inventory (BDI; Beck and Steer, 1987; Beck et al., 1988) was given at the beginning of each testing session.

2.3.2.2 Psychosis For SS, psychotic symptoms were assessed before each testing session using the Positive and Negative Symptoms Scale for Schizophrenia (PANSS; Kay, Fiszbein, & Opler, 1987).

2.3.2.2 Adverse Events Study medication-related adverse events were assessed using the Adverse Events Checklist (George et al., 2002b).

2.3.3 Study Medication Procedures and Plasma Nicotine Determination— Mecamylamine hydrochloride (MEC; Inversine[®]), as 2.5 mg tablets and matching placebo, were obtained from Layton BioSciences, Inc (Sunnyvale, CA) under an investigational new drug license (#58,680) for its use in neuropsychiatric disorders. Study medication was administered as two tablets twice daily under double-blind conditions (see Sacco et al., 2005). Venous plasma for nicotine and its metabolite cotinine were obtained at Day 2AM (0900h), and repeated at Day 3AM (0900h) and Day 3PM (1300h; 1-hour after beginning cigarette smoking reinstatement). Whole blood was obtained using sterile procedures by a trained phlebotomist and samples were collected in EDTA (K2) Sterile tubes. Within 5 minutes, blood was centrifuged at 5,000 g using a refrigerated ultracentrifuge $\times$ 10 minutes, and then plasma was removed from cellular blood components and stored at -80 degrees Celsius for later analysis. Nicotine and cotinine concentrations (ng/ml) were determined by reversed-phase high performance liquid chromatography (HPLC) procedures adapted from Hariharan and colleagues (Hariharan et al., 1988).

2.4 STATISTICAL METHODS

2.4.1 Demographics and Adverse Events—Independent samples t-tests were used to compare SS and CS on continuous demographic variables (e.g., age). Chi Square or Fisher's Exact Tests were used for categorical demographic variables (e.g., sex) and adverse events.

2.4.2 Study Aim #1—Independent samples t-tests were used to compare SS and CS on baseline smoking and clinical measures. Because the SS included a higher proportion of African-American participants, a stepwise regression analyses was run to examine differences

in cotinine/CPD ratio and nicotine/CPD ratio by race. Race and diagnosis were entered as independent variables. Cotinine/CPD ratio was entered as the dependent variable in the first analysis and nicotine/CPD ratio was entered as the dependent variable in the second analysis.

2.4.3 Study Aims #2, 3, and 4—For smoking measures and the BDI, a series of $2 \times 3 \times 3$ mixed factor analyses of variance (ANOVAs) were run with diagnosis as the between-subjects variable with two levels (SS, CS) and Session and MEC dose as within-subject variables each with three levels (Session: Day 2AM, Day 3AM, Day 3PM; MEC dose: 0.0, 5.0, 10.0 mg/day). For PANSS, 3×3 ANOVAs (Session $\times$ MEC Dose) were conducted in SS.

For all main effect analyses in the ANOVA models, statistical significance was defined with $p < .05$. For planned post hoc comparisons across test sessions and MEC dose, a Bonferroni-corrected $\alpha = 0.05/3 = 0.0167$ was used to define statistical significance. Analyses were performed using Statistical Packages for Social Sciences (SPSS) software v.12.0 for Windows.

3. RESULTS

3.1 Demographics of Study Groups

There were no significant differences between the SS and CS on age, sex, or race. SS reported fewer years of education than CS (see Table 1).

SS were stabilized on antipsychotic medication [$n=20$ on atypical and $n=7$ on typical antipsychotics]. Mean chlorpromazine equivalents, a measure of overall antipsychotic drug dose (Woods, 2003), were comparable to those reported previously (George et al., 2002a).

3.2 Baseline Smoking and Clinical Measures in Schizophrenia and Control Smokers

SS and CS did not differ on baseline measures of average consumption of cigarettes per day, CO level, or level of nicotine dependence. SS also did not differ from CS on baseline craving (TQSU Factor 1 and 2) or withdrawal (M-NWS) (see Table 1).

SS had significantly higher baseline plasma nicotine levels, plasma cotinine levels, nicotine/CPD ratio, and cotinine/CPD ratio than CS (see Table 1). Regression analysis suggested that diagnosis accounted for 15.5% of the variance ($p < .01$) and race accounted for an additional 7.4% of the variance in the cotinine/CPD ratio (full model, $p < .01$). Analysis of the nicotine/CPD ratio suggested that diagnosis accounted for 17% of the variance ($p < .01$). Race contributed an additional 5.6% which did not add a significant amount of variance (full model, $p = 0.09$).

SS had lower Shipley IQ scores and reported higher levels of depression. CS reported minimal symptoms while SS reported symptoms in the low end of the mild range (BDI score ~ 10 ; Beck et al., 1988). For SS, symptoms of schizophrenia fell in the mild-moderate range (Kay et al., 1987; Table 1).

3.3 Effects of Abstinence, Reinstatement, and MEC on Smoking and Clinical Measures in Smokers with and without Schizophrenia

3.3.1 Smoking Measures

3.3.1.1 Comparison of Cigarettes Smoked During the Smoking Reinstatement Period: Effects of MEC Dose (Figure 2). In the placebo condition (0.0 mg/day), SS smoked significantly more cigarettes during the smoking reinstatement period [SS 3.7 ± 1.8 ; CS 2.6 ± 0.8 ; $t = 2.47$; $df = 25.66$; $p < .05$]. MEC did not significantly alter smoking consumption. However, there was a nearly significant difference in number of cigarettes consumed by SS versus CS during the reinstatement period at the 5.0 mg/day dose ($p = 0.08$) (Figure 2).

3.3.1.2 Plasma Nicotine and Cotinine Levels, and Expired CO Levels For plasma nicotine levels (in ng/ml), the main effects of Diagnosis [$F = 15.79$; $df = 1, 358$; $p < .001$], Session [$F = 196.97$; $df = 2, 358$; $p < .001$], and the Diagnosis $\times$ Session interaction were significant [$F = 3.86$; $df = 2, 358$; $p < .05$]. SS reported higher levels of nicotine at baseline ($p < 0.05$; see Table 1). Bonferroni-corrected post hoc tests revealed that plasma nicotine levels decreased to a negligible level after overnight abstinence ($ps < .001$) then significantly increased after smoking reinstatement ($ps < .001$). This pattern was the same for both SS and CS [SS Smoking Baseline 32.3 ± 16.6 ng/ml; Overnight Abstinence 2.8 ± 3.7 ng/ml; Smoking Reinstatement 25.5 ± 11.4 ng/ml; CS Smoking Baseline 22.9 ± 15.0 ng/ml; Overnight Abstinence 0.70 ± 2.4 ng/ml; Smoking Reinstatement 22.6 ± 9.8 ng/ml; $F = 3.86$; $df = 2, 358$]. MEC dose had no effect on nicotine levels.

There were significant main effects of Diagnosis [$F = 28.13$; $df = 1, 398$; $p < .001$] and Session [$F = 5.07$; $df = 2, 398$; $p < .01$] for plasma cotinine levels. Plasma cotinine levels significantly decreased for both groups after overnight abstinence from smoking ($ps < .01$) and nonsignificantly increased after smoking reinstatement CS [SS Smoking Baseline 433 ± 200 ng/ml; Overnight Abstinence 350 ± 199 ng/ml; Smoking Reinstatement 366 ± 202 ng/ml; CS Smoking Baseline 295 ± 178 ng/ml; Overnight Abstinence 260 ± 187 ng/ml; Smoking Reinstatement 291 ± 201 ng/ml; $F = 3.86$; $df = 2, 358$]. No other differences by session were significant. MEC had no effect on cotinine levels.

Expired breath carbon monoxide (CO) levels (in ppm) showed the expected pattern of decreasing during abstinence and increasing after smoking reinstatement for both SS and CS. MEC dose did not affect CO levels.

3.3.1.3 Tobacco Craving: TQSU Factor 1 For tobacco craving level as measured by the TQSU Factor 1, a significant main effect for Session was found [$F = 34.61$; $df = 2, 477$; $p < .001$]. Craving level increased after overnight abstinence ($ps < .001$) and decreased after smoking reinstatement ($ps < .001$) for both SS and CS. MEC dose did not alter baseline craving levels, nor cravings during smoking abstinence and reinstatement.

3.3.1.4 Tobacco Craving: TQSU Factor 2 Factor 2 showed significant main effects for Diagnosis [$F = 4.60$; $df = 1, 477$; $p < .05$], and Session [$F = 16.02$; $df = 2, 477$; $p < .001$]. Craving levels increased significantly after overnight abstinence ($ps < .001$) and significantly decreased after smoking reinstatement ($ps < .001$) for both SS and CS. MEC dose did not alter cravings at baseline nor after abstinence or reinstatement.

3.3.1.5 Nicotine Withdrawal For M-NWS total score, the main effect of Diagnosis [$F = 6.77$; $df = 1, 454$; $p = .01$] was significant. There were no significant changes in withdrawal scores over abstinence and reinstatement or by MEC dose. Similar analyses with M-NWS individual items showed a significant effect of Session for the experience of cravings [$F = 10.17$; $df = 2, 437$; $p < .001$]. For both SS and CS, craving levels significant increased after overnight abstinence ($ps < .001$) and significantly decreased after smoking reinstatement ($ps < .001$). There were no other significant changes by session for other withdrawal symptoms.

3.3.2 Psychiatric Symptoms

3.3.2.1 Symptoms of Depression The 3-way interaction of Diagnosis $\times$ Session $\times$ MEC dose was not significant for BDI scores. There was only a main effect of Diagnosis on symptoms of depression [$F = 140.6$ $df = 1, 482$; $p < .001$].

3.3.2.1 Psychotic Symptoms For SS, Session $\times$ MEC dose interactions were not significant and there were no main effects of Session or MEC dose for any of the PANSS subscores.

3.4 Adverse Events Related to Study Medication

Although there were high rates of known side effects of MEC (e.g., dry mouth, urinary hesitation, dizziness, constipation), the only side effect that showed significant dose-dependent effects of MEC was constipation in the CS ($p < 0.01$). There were no serious or unanticipated adverse events with the study medication during the study.

4. DISCUSSION

The main goals of this study were to determine similarities and differences between smokers with schizophrenia (SS) and control smokers (CS) on biochemical and behavioral indices of smoking during: 1) non-deprived baseline state (Day 2AM), and; 2) after overnight (16 hour) abstinence (Day 3AM) and after smoking reinstatement (Day 3PM). Additional aims were to investigate the effects of 3) abstinence and reinstatement on psychiatric symptoms, and; 4) MEC administration on study outcomes.

4.1 Baseline Differences

Despite being matched on daily smoking and nicotine dependence, SS had significantly higher levels of plasma nicotine, plasma cotinine, nicotine/CPD, and cotinine/CPD ratio (a measure of nicotine extraction). Differences in cotinine and nicotine levels between SS and CS were not associated with differences in cravings or withdrawal symptoms.

Our finding of a higher plasma cotinine level per cigarette smoked (cotinine/CPD ratio) is consistent with earlier studies that reported higher urinary, plasma and saliva cotinine levels (Olincy et al., 1997; Sacco et al., 2005; Strand and Nybäck, 2005; Williams et al., 2005) and greater reward value (Spring et al., 2003) in SS. Olincy et al. (1997) found no differences between groups in urinary cotinine clearance, while Williams et al. (2005) showed that the ratio of 3-hydroxycotinine (a metabolite of cotinine) to cotinine was not altered in SS suggesting increased nicotine intake rather than alterations in nicotine metabolism. Reduced high-affinity nAChR expression in postmortem schizophrenic brain in limbic structures such as striatum, hippocampus, thalamus and prefrontal cortex has been found (Breese et al., 2000) may render patients with schizophrenia less sensitive to nicotine's effects, leading to compensatory increases in nicotine intake.

African-Americans have higher cotinine levels (Caraballo et al., 1998; Wagenknecht et al., 1990), and slower cotinine clearance and higher intake of nicotine per cigarette than Caucasians (Perez-Stable et al., 1998). Regression analysis suggested that diagnostic group explained a larger portion of the variance than race; however, this analysis was limited by small sample sizes.

4.2 Effect of MEC Pre-treatment on Smoking Indices and Psychiatric Outcomes

nAChR blockade by MEC did not significantly impact any biochemical or behavioral indices of smoking, nor depressive or psychotic symptoms. The lack of effects of MEC are consistent with a previous report that acute MEC administration at doses of up to 20 mg/day did not precipitate tobacco withdrawal in dependent cigarette smokers (Eissenberg et al., 1996), and extends the lack of MEC pre-treatment effects on cigarette withdrawal and craving to a subchronic (e.g., six doses over a three day period) dosing paradigm, in which MEC plasma levels presumably reached steady state (the half-life of MEC is ~10 hours; Young et al., 2001). Several studies in cigarette smokers have demonstrated that acute doses of MEC in the dose range used in the present study (5-10 mg/day) increase cigarette smoking (Stolerman et al., 1973; Nemeth-Coslett et al., 1986; Pomerleau et al., 1987; Rose et al., 2001), suggesting a compensatory increase in smoking behavior in the presence of a nicotinic antagonist. At the first testing session (Day 2AM), SS and CS had received three doses of MEC, but there was

no alteration in the amount of cigarettes smoked or in baseline nicotine or cotinine levels. Compensation in amount of cigarette smoking in response to acute MEC exposure may have been extinguished with repeated drug administration. Similarly, acute MEC pre-treatment has been shown to increase intravenous nicotine self-administration in humans (Rose et al., 2003). In contrast, MEC administration precipitates nicotine withdrawal in nicotine-dependent rodents (Hildebrand et al., 1997; Malin et al., 1994). The finding that MEC did not alter craving and withdrawal suggests that other factors besides nicotine (e.g., tar) may play a role in these subjective effects of cigarette smoking (Dallery et al., 2003; Rose and Behm, 2004).

4.3 Effects of Smoking Abstinence and Reinstatement on Smoking Measures

SS and CS showed a similar pattern of response to overnight abstinence and smoking reinstatement. However, we did note that SS consumed significantly more cigarettes than CS after overnight abstinence which is consistent with prior reports of enhanced reinforcement in SS (Spring et al., 2003). For all smokers, craving level increased with abstinence and decreased with reinstatement of smoking while plasma nicotine decreased with abstinence and increased with reinstatement. Changes in plasma cotinine were less robust than with nicotine, likely due to its long half-life (~16-20 hours) (Benowitz et al., 2002). Significant withdrawal symptoms did not emerge, which may be attributed to the relatively short period of abstinence (16 hours). Symptoms of nicotine withdrawal are clinically significant within 24 hours and most severe after 2-4 days of smoking abstinence (Hughes and Hatsukami, 1986). In addition, factors such as the absence of smoking cues (Buchhalter et al., 2005) in the laboratory setting could have contributed to the minimal withdrawal symptoms.

4.4 Effects of Abstinence and Reinstatement on Psychiatric Symptoms

Overnight abstinence and reinstatement did not increase depressive symptoms in SS or CS, or psychotic symptoms in SS. Previous work found no significant changes in positive or negative symptoms of schizophrenia over three days of acute abstinence (Dalack et al., 1999) and no change in positive symptoms for patients who quit smoking during 10-week trials of nicotine patch (George et al., 2000) or bupropion (George et al., 2002b). Together, these results suggest that abstinence from cigarettes for several weeks does not significantly alter psychotic symptoms in patients with schizophrenia.

4.5 Implications

SS and CS showed similarities on several smoking indices at smoking baseline, and after abstinence and reinstatement. However, our findings suggest that SS may experience enhanced cigarette smoking reinforcement and greater extraction of nicotine than CS which require further investigation. Understanding such differences in smoking behaviors may lead to targeted and more effective pharmacological and behavioral interventions for nicotine dependence in patients with schizophrenia.

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Figure 1.
Single Subject Study Timeline for Smokers with Schizophrenia and Control Smokers

* $p < 0.05$ for comparison of SS versus CS at 0.0 mg/day dose

Figure 2. Comparison of Smokers with Schizophrenia (SS; n=27) and Control Smokers (CS; n=26) and the effects of MEC Dose on total number of cigarettes smoked during the 1-hour smoking reinstatement session.

Table 1

Demographic, Clinical, and Smoking Characteristics of Smokers with Schizophrenia (SS; n=27) and Control Smokers (CS; n=26).

Variable	SS (N=27)	CS (N=26)	p-value
Demographic Variables			
Age (years)	41.8 ± 8.9	40.9 ± 10.9	<i>p</i> =0.74
Sex	15 M/ 12 F	12M/ 14 F	<i>p</i> =0.49
Race	12 C/ 13 AA/ 2 O	18 C/ 6 AA/ 2 O	<i>p</i> =0.15
Education (years)	12.0 ± 2.4	14.0 ± 3.0	<i>p</i> <0.05
Psychotic Diagnosis	19 SCZ/ 8 SCA	n/a	-----
Behavioral Smoking Measures			
Cigarettes Per Day (CPD)	21.7 ± 11.7	21.5 ± 5.8	<i>p</i> =0.77
FTND Score	6.6 ± 1.5	6.4 ± 1.5	<i>p</i> =0.62
T-QSU Factor 1	4.2 ± 1.3	4.7 ± 1.3	<i>p</i> =0.10
T-QSU Factor 2	3.3 ± 1.5	3.4 ± 1.3	<i>p</i> =0.76
M-NWS	15.5 ± 11.3	14.2 ± 11.5	<i>p</i> =0.71
Biochemical Smoking Measures			
Expired Breath CO level (ppm)	22.1 ± 9.0	20.3 ± 9.4	<i>p</i> =0.48
Baseline Plasma Nicotine (ng/ml)	31.2 ± 16.0	21.8 ± 11.4	<i>p</i> <0.05
Nicotine/CPD ratio	1.4 ± 1.4	1.0 ± 2.0	<i>p</i> <0.01
Baseline Plasma Cotinine (ng/ml)	432 ± 198	275 ± 101	<i>p</i> <0.01
Cotinine/CPD ratio	19.9 ± 16.9	12.8 ± 17.4	<i>p</i> <0.05
Psychiatric Measures			
Shipley IQ	84.5 ± 14.1	101.4 ± 12.2	<i>p</i> <0.01
BDI score	10.5 ± 8.7	4.1 ± 3.2	<i>p</i> <0.01
PANSS			
Positive	13.9 ± 2.2	n/a	-----
Negative	12.8 ± 3.0	n/a	-----
General	28.1 ± 4.2	n/a	-----
Total	54.7 ± 7.8	n/a	-----

Note: Data on age, sex, race, education, IQ and FTND were collected during the baseline screening process. Data on T-QSU, M-NWS, CPD, CO, BDI, and PANSS and nicotine and cotinine levels were derived from the Day 2AM session of the placebo condition (MEC dose = 0.0 mg/day).

Abbreviations: CPD, Cigarettes Per Day; CO, Carbon Monoxide; FTND, Fagerstrom Test for Nicotine Dependence; T-QSU, Tiffany Questionnaire on Smoking Urges; M-NWS, Minnesota Nicotine Withdrawal Scale; BDI, Beck Depression Inventory; Shipley IQ Scores from the Weschler Adult Intelligence Scale-Revised; PANSS, Positive and Negative Symptoms Scale for Schizophrenia; SCZ, Schizophrenia; SCA, Schizoaffective disorder.